The Living State

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That our body is composed of organs was discovered by the anatomists of the Renaissance. That these organs are composed of cells was discovered by the microscopists of the nineteenth century. That the cells are composed of molecules was established by the present biology, which is molecular biology.

Molecules are composed of atoms, and atoms of electrons and nuclei, which are composed of still smaller units. How far this subdivisibility of Nature continues we do not know, but as far as biology is concerned we have reached the bottom with electrons, because further subdivision involves enormous energies that can destroy cities or the whole of mankind, but no longer fit into the realm of biology. So in biology we are faced with four dimensions only: macroscopic, microscopic, molecular, and electronic. Biology has followed through as far as the molecular dimension, but has failed to penetrate into the electronic dimension. This is why we cannot solve simple problems, such as the nature of cancer or the biological function of ascorbic acid. We have to look for the answers in the electronic dimension, using the broad outlook of natural philosophy.

What distinguishes the *animate* (alive) from the *inanimate* (not alive) is the subtle reactivity of living systems. Since the main bearers of life are proteins, one would expect proteins to show a similar subtle reactivity. They do not. This is a gap between the living and nonliving that has to be bridged before the problem of cancer and the function of ascorbic acid can be solved. If proteins are the main bearers of life, then, in the living organism, some of them must have a high reactivity, and be in a specific physicochemical state that we will call *the living state*.

Proteins consist of "macromolecules." Such macromolecules may be 1000 times smaller than the smallest thing we can see, but for the chemist they are still very clumsy, unwieldy formations. Each of the atoms consists of a nucleus, surrounded by electrons that form pairs, the two electrons of a pair spinning in opposite directions. The magnetic moments of the two electrons compensate for one another and strongly couple the two electrons. In a protein molecule all orbitals are occupied, leaving no room for motion. The situation is analogous to a completely filled parking lot, where there can be no movement. All this makes a pure protein molecule into a clumsy, unreactive unit that has nothing of the wonderful reactivity of living systems.

There is one way in which such a molecule can be endowed with a high reactivity and electronic mobility, and this is by desaturating it electronically by removing a single electron from it. To remove an electron from the molecule an

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electron pair has to be separated, or uncoupled. The eliminated electron leaves a positively charged "hole" and a half-occupied orbital behind. This upsets the balance of the whole molecule and makes room for motion, as taking out a car from a filled parking lot makes all cars mobile. Molecules that contain an unpaired electron are *free radicals,* which are known to be very reactive. Our first question thus has to be: how can single electrons be removed from a protein molecule? Needless to say, not all cellular protein molecules have to be transformed into free radicals. Proteins are wonderfully versatile substances and fill different jobs in cell life, many of which are very simple and demand no special reactivity.

Electrons can be removed from protein molecules by other molecules that have an empty orbital on which they can accommodate an additional electron. Such molecules are *electron acceptors.* If the empty place has a lower energy than the electron we want to transfer onto it, then the electron will be donated spontaneously, if the two molecules come into a sufficiently intimate contact. The transfer of an electron from one molecule to another is *charge transfer.* The protein has to act in this process as an *electron donor.* The acceptor used by Nature is methylglyoxal. It was discovered more than 60 years ago that, apparently, all living systems contain a most powerful enzymatic system for the inactivation of methylglyoxal. So this substance must have had something very important to do, but no one could discover what.

Methylglyoxal can attack protein by interacting with its NH_2. But because proteins are very complex substances, we began by studying this reaction using simpler amines. We used methylamine, the simplest aliphatic amine.

When we mixed a watery solution of methylglyoxal and methylamine, a dark color developed, indicating an interaction. As shown by Gascoyne in the ESR spectroscope, the dark solution gave a strong signal, which meant that the sample contained uncoupled electrons; electron pairs having been separated, single electrons going from methylamine to methylglyoxal. Charge transfer had taken place. If the experiment was repeated in the presence of a small amount of ascorbate, the color developed faster and the ESR signal was much stronger. This indicated that ascorbic acid promotes one of the most fundamental reactions of biology—the reaction by which protein is desaturated and transduced into the *living state.*

It is natural to ask whether this charge transfer is connected with optical changes, i.e., the development of a new absorption. When methylglyoxal and methylamine interact, various-colored compounds can be formed, which makes spectroscopy difficult; but the action of ascorbate made differential spectroscopy possible and revealed the spectral change as being due to ascorbate. We only had to find the difference in the absorption of a solution that contained ascorbate with one that contained none (placing the former into the primary, the latter into the reference beam of the spectroscope). Under these circumstances, the instrument measured only the difference between the two absorptions due to ascorbic acid. We found that under these circumstances ascorbate made a strong new absorption appear with a high and narrow peak around 380 nm. The ab-

sorption increased with increasing ascorbate concentration without reaching a maximum within the measurable range: the more ascorbate there was, the better it could transduce the protein into the living state. On this point ascorbic acid differs from other vitamins, which have a beneficial action only as long as they correct a deficiency. Ascorbic acid acts better the more there is of it. The more we have the better off we are. This supports the claims of Stone [1], Pauling [2] and of Klenner [3] for using megadoses of ascorbic acid. "More alive" means that we can better meet any stress or infection, and ascorbic acid may support us in any pathological condition.

The next task had to be to clarify the chemical mechanism by which ascorbate promoted the charge transfer between methylamine and methylglyoxal. The road to understanding was opened by Gascoyne's observation that solid sodium ascorbate, dissolved in water, gave a strong ESR signal, but did so only if oxygen was present. In the absence of O_2 there was no signal; on admission of O_2 the signal appeared. A signal indicates the presence of free radicals, unpaired electrons. This indicated that the ascorbate entered charge transfer with O_2 and donated an electron to it. The ascorbate radical, thus formed, had an empty place on which it could accept an electron from methylamine or an amino group of protein. The electron of the protein is accepted by methylglyoxal, which then passes it to the ascorbate radical, that has made room for it by having donated one of its electrons to oxygen. This means that the final electron acceptor for protein is O_2, which has far-reaching consequences for biology and medicine. It is oxygen that transduces protein into the living state.

In a mixture of methylamine and methylglyoxal in the absence of ascorbate and O_2, a relatively weak absorption appears at 380 nm. This absorption indicated that methylglyoxal can desaturate protein to some extent in the absence of ascorbate and O_2 also, but can do so only very poorly. This is important because there was also life on this planet before oxygen appeared, only it had to be a very poor and primitive life. Life began to develop and differentiate when oxygen and ascorbate appeared and opened the way to higher forms of life. This also explains how life can survive on very low levels of ascorbic acid. The young can do so especially, although not even they can do it unpunished. The ability to desaturate protein at low levels of ascorbate decreases with age.

The question may be asked: do the NH_2 groups of protein react in the same way as those of methylamine? To test this we repeated our experiments with protein, instead of methylamine. The proteins used were caseine and serum albumin. We could repeat practically everything with protein, and Bone et al. [4] showed that the protein treated with methylglyoxal became an electronic conductor, i.e., had its electrons mobilized.

Proteins are, essentially, long chains of "peptide links" held together by single carbon atoms. The peptide links themselves are small and flat units consisting of three atoms, an O, a C, and an N. If we write "P" for the peptide link, then the protein can be symbolized by ···CPCPCPCPCPCP···. The NH_2 groups are introduced into this molecule by the diamino acids: lysine and arginine. The

NH_2 group of lysine is situated at the end of a four-carbon-atom chain, which hangs out sideways, as shown in Figure 1.

Methylglyoxal, acting as acceptor in the desaturation of protein, attaches itself to NH_2. A covalent bond is formed between the two, which means that methylglyoxal has become part of the protein molecule; incorporated into it. Methylglyoxal has a low-lying empty orbital on which it can accommodate an additional electron. What Nature does is thus to induce mobility into the electrons of the protein by incorporating an electron acceptor into the molecule. A closely analogous process is widely used in semiconductor industry in the construction of radio, television, or computers. It is called *doping*. It is the most basic process of that industry. Nature discovered it billions of years before man did. If electrons are transferred from the protein on to methylglyoxal and are incorporated into it, the electrons are moved inside the protein molecule without producing net charges.

An objection could be raised that, to make protein conductant, electrons have to be removed from the main peptide chain, and not from the side groups, which are isolated from the main chain. But the carbon chain, which holds the NH_2 groups at its end, is pliable and can fold up, bringing the methylglyoxal's and ascorbate radicals attached to the NH_2s into direct contact with the neighboring peptide bonds from which they can accept electrons. Protein could thus also be desaturated to some extent before light, O_2, and ascorbic acid appeared, producing a low degree of desaturation that made the existence of primitive forms of life possible. The appearance of light led to the production of oxygen, and oxygen could take, through ascorbate, a whole electron from methylglyoxal and protein, leading to a strong desaturation, which led to the building of higher forms of life. Many proteins contain 12% lysine, which means that every eighth amino acid is lysine and the peptide chain has a boosting station for its desaturation at every eighth amino acid.

The electronic desaturation of protein has a profound influence on the nature of the protein molecule by making its electrons mobile. Laki and Ladik [6] found that the desaturation of protein also increases the interaction between peptide chains, increasing the cohesive forces that hold our cells together several orders of magnitude. In the absence of ascorbic acid these forces are insufficient and our body disintegrates, as it actually does in scurvy. As is generally known, in scurvy old scars reopen. Old scars are composed of collagen and so their reopening cannot be due to the lack of collagen but has to be due to weakening of the cohesive forces holding the collagen fibers together.

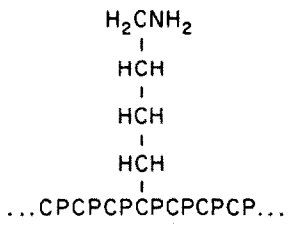

Figure 1. A peptide chain.

The failure of the chemical mechanism of desaturation can lead to various pathological conditions. The extensive studies in this laboratory, pursued during the last decades, have led to the conclusion that what goes wrong in cancer is the chemical mechanism of this desaturation. These studies also led to a better understanding of the history of life, which can be divided into two parts by the appearance of light, oxygen, and ascorbic acid into a first primitive, dark, and anaerobic part, which we called the α period, and a light, aerobic part of development and differentiation, which we call the β period. The end result of this development and differentiation is mankind. The result of a return to the α state is cancer.

Laki and Ladik's results indicate that to be able to build a healthy well-constructed body we need a generous supply of ascorbic acid. We need it all the time, not only when a cold threatens. I strongly believe that a wider use of ascorbic acid could greatly improve our vital statistics and also cut down on cancer.

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